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Ruthenium-catalyzed synthesis of amides from alcohols and amines: mechanistic study and application

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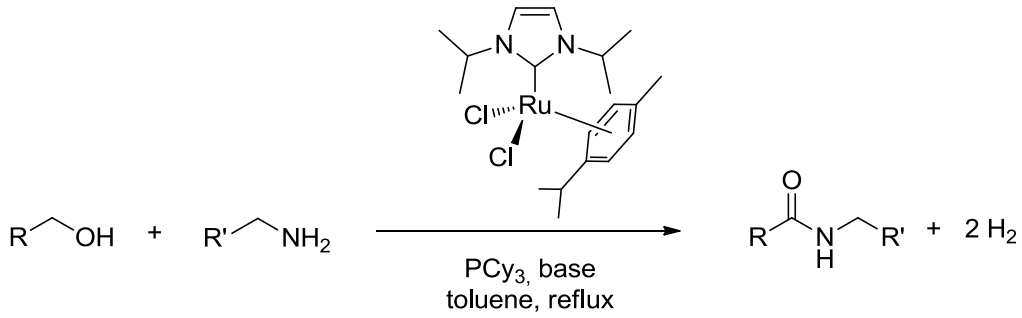
The amide bond is one of the most important linkages in organic chemistry and constitutes the key functional group in peptides, polymers and many pharmaceuticals.[1, 2] Amides are often synthesized by coupling of carboxylic acids or its derivatives with amines. In spite of their efficiency these methods are not environmentally friendly since toxic reagents are used and a lot of waste is produced. Development of new synthetic methods which are both efficient and "green" continues to receive significant attraction. Recently in Madsen group a new method for amide synthesis has been discovered where alcohols and amines are coupled directly with the liberation of hydrogen gas.[3, 4] (Scheme 1).



Scheme 1. Ruthenium-catalyzed amide synthesis.

In the present work an experimental and theoretical mechanistic investigation of this reaction has been carried out. In the experimental part various kinetic aspects of the reaction were studied. Para-substituted benzyl alcohols were used as substrates to elucidate the electronic influence of the *para* substituent on the reactivity, *i.e.* a Hammett study. Deuterium-labeled substrates were employed to probe the kinetic isotope effect. By using DFT calculations with the M06 functional, energetic and structural parameters were determined for the intermediates and transition states in the proposed catalytic cycle. From the experimental and theoretical studies the rate determining step was established which is important for further optimization of the reaction.

References:

1. V. R. Pattabiraman, J. W. Bode, *Nature*, 2011, **480**, 471-479.
2. J. W. Bode, *Curr. Opin. Drug Discov. Dev.* 2006, **9**, 765-775
3. L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672-17673.
4. J. H. Dam, G. Osztrovszky, L. U. Nordstrøm, R. Madsen, *Chem. Eur. J.*, 2010, **16**, 6820-6827.